



REVIEW ARTICLE



Japanese Lung Cancer Society Guidelines for Stage IV NSCLC With *EGFR* Mutations

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ABSTRACT

Patients with NSCLC in East Asia, including Japan, frequently contain *EGFR* mutations. In 2018, we published the latest full clinical practice guidelines on the basis of those provided by the Japanese Lung Cancer Society Guidelines Committee. The purpose of this study was to update those recommendations, especially for the treatment of metastatic or recurrent *EGFR*-mutated NSCLC. We conducted a literature search of systematic reviews of randomized controlled and nonrandomized trials published between 2018 and 2019 that multiple physicians had reviewed independently. On the basis of those studies and the advice from the Japanese Society of Lung Cancer Expert Panel, we developed updated guidelines according to the Grading of Recommendations, Assessment, Development, and Evaluation system. We also evaluated the benefits of overall and progression-free survival, end points, toxicities, and patients' reported outcomes. For patients with NSCLC harboring *EGFR*-activating mutations, the use of *EGFR* tyrosine kinase inhibitors (*EGFR* TKIs), especially osimertinib, had the best recommendation as to first-line treatment. We also recommended the combination of *EGFR* TKI with other agents (platinum-based chemotherapy or antiangiogenic agents); however, it can lead to toxicity. In the presence of *EGFR* uncommon mutations, except for an exon 20 insertion, we also recommended the *EGFR* TKI treatment. However, we could not provide recommendations for the treatment of *EGFR* mutations with immune checkpoint inhibitors, including monotherapy, and its combination with cytotoxic chemotherapy, because of the limited evidence present in the literature. The 2020 Japanese Lung Cancer Society Guidelines can help community-based physicians to determine the most appropriate treatments and adequately provide medical care to their patients.

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Introduction

Therapies for stage IV NSCLC are evolving day by day, and the progress achieved over the past decade has been impressive. Since 2010, the Japanese Society of Lung Cancer (JLCS) Guidelines Committee has provided treatment guidelines for community-based physicians to adequately treat their patients. Based on this, we published the latest full clinical practice guidelines in 2018.¹ In this study, we conducted a literature search and systematic review from 2018 to 2019 to update these guidelines, specifically focusing on studies that involved

mutations in the sequence encoding for *EGFR*, which is one of the most altered regions.

Materials and Methods

Process of Systematic Review

We conducted a systematic review on the basis of the Grading of Recommendations, Assessment, Development, and Evaluation system,² to develop lung cancer medical treatment guidelines in Japan. The detailed collection of these reviews is described in the [Supplementary Data](#). The recommendation (R) level was determined on the basis of the Grading of Recommendations, Assessment, Development, and Evaluation grid method³ and the votes from the JLCS Expert Panel, composed of individuals with various occupations, and whose conflicts of interest were strictly controlled according to the regulations of the JLCS.

Key Outcomes of Interest

We focused on the efficacy of overall survival (OS) and progression-free survival (PFS) as the key outcomes when assessing clinical questions (CQs). In addition, toxicity and patient-reported outcomes were evaluated according to the recommended level determined by the Expert Panel. Because of the difficulty in analyzing the cost-effectiveness in the Japanese universal health insurance system, the impact of treatment costs was not reflected in this set of guidelines. The voting results for each CQ provided by the Expert Panel are summarized in [Supplementary Tables 4 to 11](#). The objectivity of the guidelines was also enhanced through public comments to the JLCS members in July 2020.

Results

Characteristics of the Identified Studies

Six nonrandomized and 18 randomized controlled trials (RCTs) summarized in [Tables 1 and 2](#) met our criteria for study selection as they assessed CQs in patients with NSCLC harboring *EGFR* mutations. Besides the RCTs analyzed when we created the guidelines published in 2018,¹ we included six new RCTs and updated the results of two RCTs. In addition, we recently analyzed two exploratory RCTs: (1) the combination therapy with an immune checkpoint inhibitor (ICI); and (2) cytotoxic chemotherapy targeting *EGFR* mutations (one including *ALK* fusions) (summarized in [Table 3](#)). In this review, three meta-analysis studies were performed on each CQ using multiple RCTs with the same design, and the resulting funnel plots are illustrated in [Supplementary Figures 1 to 3](#). In contrast, for the analysis of the efficacy of ICI monotherapy, we adopted a high-quality meta-analysis already published.⁴ The quality assessments of all the included interventional studies are provided in

Table 1. Characteristics of RCTs

Study	Design	No.	Patient	Intervention	Comparison	Median Follow-Up (Updated)
Mitsudomi et al., 2010 ¹⁰ (WJTOG3405)	Phase 3	172	NSCLC harboring <i>EGFR</i> mutation (19del or L858R), 75 y or younger, stage IIIB/IV or rec, ECOG PS 0-1, treatment-naive	Gefitinib	Cisplatin plus docetaxel	81 d (59.1 mo) ¹¹
Maemondo et al., 2010 ¹² (NEJ002)	Phase 3	228	NSCLC harboring <i>EGFR</i> mutation, 75 y or younger, stage IIIB/IV or rec, ECOG PS 0-1, treatment-naive	Gefitinib	Carboplatin plus paclitaxel	527 d (704 d) ¹³
Zhou et al., 2011 ¹⁴ (OPTIMAL)	Phase 3	154	NSCLC harboring <i>EGFR</i> mutation (19del or L858R), 18 y or older, stage IIIB/IV or rec, ECOG PS 0-2, treatment-naive	Erlotinib	Carboplatin plus gemcitabine	15.6 mo (25.9 mo) ¹⁵
Rosell et al., 2012 ¹⁶ (EURTAC)	Phase 3	174	NSCLC harboring <i>EGFR</i> mutation (19del or L858R), 18 y or older, stage IIIB/IV, ECOG PS 0-2, treatment-naive	Erlotinib	Platinum-doublet ^a	18.9 mo (Not described) ¹⁷
Wu et al., 2015 ¹⁸ (ENSURE)	Phase 3	217	NSCLC harboring <i>EGFR</i> mutation (19del or L858R), 18 y or older, stage IIIB/IV, ECOG PS 0-2, treatment-naive	Erlotinib	Cisplatin plus gemcitabine	27.1-28.9 mo
Sequist et al., 2013 ¹⁹ (LUX-Lung 3)	Phase 3	345	Lung adenocarcinoma harboring <i>EGFR</i> mutation, 18 y or older, stage IIIB/IV, ECOG PS 0-1, treatment-naive	Afatinib	Cisplatin plus pemetrexed	16.4 mo (41 mo) ²¹
Wu et al., 2014 ²⁰ (LUX-Lung 6)	Phase 3	364	Lung adenocarcinoma harboring <i>EGFR</i> mutation, 18 y or older, stage IIIB/IV, ECOG PS 0-1, treatment-naive	Afatinib	Cisplatin plus gemcitabine	16.6 mo (33 mo) ²¹
Soria et al., 2018 ²⁵ (FLAURA)	Phase 3	556	NSCLC harboring <i>EGFR</i> mutation (19del or L858R), 18 y or older, locally advanced, or metastatic, ECOG PS 0-1, treatment-naive	Osimertinib	Gefitinib or erlotinib	15.0 mo (35.8 mo) ²⁶
Hosomi et al., 2020 ²⁷ (NEJ009)	Phase 3	345	Non-SCC NSCLC harboring <i>EGFR</i> mutation (exons19, 21, or 18), 20 y or older, stage IIIB/IV or rec, ECOG PS 0-1, treatment-naive	Gefitinib plus CBDCA/PEM	Gefitinib	45 mo
Noronha et al., 2020 ²⁸	Phase 3	350	NSCLC harboring <i>EGFR</i> mutation (exons19, 21, or 18), 18 y or older, stage IIIB/IV, ECOG PS 0-2, treatment-naive	Gefitinib plus CBDCA/PEM	Gefitinib	17 mo
Seto et al., 2014 ²⁹ (JO25567)	Phase 2	152	Non-SCC NSCLC harboring <i>EGFR</i> mutation (19del or L858R), 20 y or older, stage IIIB/IV or rec, ECOG PS 0-1, treatment-naive	Erlotinib plus bevacizumab	Erlotinib	20.4 mo (34.7 mo) ³⁰
Saito et al., 2019 ³¹ (NEJ026)	Phase 3	224	non-SCC NSCLC harboring <i>EGFR</i> mutation (19del or L858R), 20 y or older, stage IIIB/IV or rec, ECOG PS 0-2, treatment-naive	Erlotinib plus bevacizumab	Erlotinib	12.4 mo (39.2 mo) ³²
Stinchcombe et al., 2019 ³³	Phase 2	88	NSCLC harboring <i>EGFR</i> mutation (19del or L858R), stage IV, ECOG PS 0-1, treatment-naive	Erlotinib plus bevacizumab	Erlotinib	33 mo
Nakagawa et al., 2019 ³⁴ (RELAY)	Phase 3	449	NSCLC harboring <i>EGFR</i> mutation (19del or L858R), 18 y or older, stage IV, or rec, ECOG PS 0-1, treatment-naive	Erlotinib plus ramucirumab	Erlotinib plus placebo	20.7 mo
Wu et al., 2017 ³⁵ (ARCHER1050)	Phase 3	452	NSCLC harboring <i>EGFR</i> mutation (19del or L858R), 18 y or older, stage IIIB/IV, ECOG PS 0-1, treatment-naive, no brain metastases	Dacomitinib	Gefitinib	22.1 mo (31.3 mo) ³⁶

(continued)

Table 1. Continued

Study	Design	No.	Patient	Intervention	Comparison	Median Follow-Up (Updated)
Yang et al., 2017 ³⁷ (CTONG0901)	Phase 3	256	NSCLC harboring <i>EGFR</i> mutation (19del or L858R), 18 y or older, advanced, or metastatic, ECOG PS 0-2, EGFR TKI naive	Erlotinib	Gefitinib	22.1 mo
Park et al., 2016 ³⁸ (LUX-Lung 7)	Phase 2	319	Lung adenocarcinoma harboring <i>EGFR</i> mutation, 18 y or older, stage IIIB/IV, ECOG PS 0-1, treatment-naive	Afatinib	Gefitinib	27.3 mo
Mok et al., 2017 ⁵⁰ (AURA3)	Phase 3	419	NSCLC harboring <i>EGFR</i> T790M resistant mutation, 18 y or older, locally advanced, or metastatic, ECOG PS 0-2, after first-line EGFR TKI therapy	Osimertinib	Platinum-doublet ^b	8.3 mo

^aCisplatin or carboplatin plus docetaxel or gemcitabine.

^bCisplatin or carboplatin plus pemetrexed.

19del, exon 19 deletion; CBDCA, carboplatin; ECOG, Eastern Cooperative Oncology Group; PEM, pemetrexed; PS, performance status; RCT, randomized controlled trial; rec, recurrent disease; SCC, squamous cell carcinoma; TKI, tyrosine kinase inhibitor.

Supplementary Tables 2 (for RCTs) and 3 (for non-randomized trials). RCTs that were not approved by the Expert Panel were not considered in the development of the current recommendations.⁵⁻⁸ One notable RCT was not approved because it was not possible to extract sufficient meta-analytical data from published literature.⁹

General Remarks

Seven phase 3 trials comparing EGFR tyrosine kinase inhibitors (TKIs) and platinum-doublet chemotherapy in

patients with NSCLC harboring *EGFR* mutations were analyzed.¹⁰⁻²¹ Among them, EGFR TKI administration consistently prolonged PFS (as the primary end point) compared with that of platinum-doublet (pooled hazard ratio [HR]: 0.34; 95% confidence interval [CI]: 0.27-0.44; $p < 0.001$); however, a strong heterogeneity in the overall PFS effect across the seven trials was noted (χ^2 : 18.40; $p = 0.005$; I^2 : 67.4%) (Fig. 1A). On the contrary, the risk of death was not significantly heterogeneous (χ^2 : 4.28; $p = 0.638$; I^2 : 0%) (Fig. 1B) or different between EGFR TKI and platinum-doublet chemotherapy

Table 2. Study Characteristics of Nonrandomized Trials

Study	Design	No.	Patient	Intervention	Median Follow-Up, mo
Inoue et al., 2009 ³⁹ (NEJ001)	Phase 2	30	NSCLC harboring <i>EGFR</i> mutation (19del, L858R, L861Q, or G719X), stage IIIB/IV or rec, poor ECOG PS (20-74 y with PS 3-4, 75-79 y with PS 2-4, and 80 y or older with PS 1-4), treatment-naive	Gefitinib	17.8
Maemondo et al., 2012 ⁴⁰ (NEJ003)	Phase 2	31	NSCLC harboring <i>EGFR</i> mutation (19del, L858R, L861Q, or G719X), stage IIIB/IV or rec, 75 y or older, ECOG PS 0-2, treatment-naive	Gefitinib	27.5
Yang et al., 2015 ⁴⁶ (LUX-lung 2,3,6)	Pooled	75	Lung adenocarcinoma harboring <i>EGFR</i> uncommon mutation (group 1; point mutation or duplications in exon18-21, group 2; de novo T790M, group 3; exon 20 insertion), 18 y or older, stage IIIB/IV, ECOG PS 0-1, treatment-naive	Afatinib	34.7
Cho et al., 2020 ⁴⁷ (KCSG-LU15-09)	Phase 2	37	NSCLC harboring <i>EGFR</i> mutation (other than 19del, L858R, T790M, or exon 20 insertions), metastatic or rec, 19 y or older, ECOG PS 0-2, EGFR TKI naive	Osimertinib	20.6
Ramalingam et al., 2018 ⁴⁹ (AURA)	Phase 1	60	NSCLC harboring <i>EGFR</i> mutation (including T790M), locally advanced or metastatic, 18 y or older, WHO PS 0-1, treatment-naive	Osimertinib	19.1

19del, exon 19 deletion; ECOG, Eastern Cooperative Oncology Group; PS, performance status; rec, recurrent disease; TKI, tyrosine kinase inhibitor.

Table 3. Characteristics of RCTs in an Exploratory Analysis

Study	Design	No. Patient	Intervention	Comparison	Median Follow-Up, mo	
Reck et al., 2019 ⁵³ (IMpower150)	Phase 3 (exploratory)	124	Non-SCC NSCLC harboring <i>EGFR</i> mutation (19del or L858R), stage IV, 18 y or older, ECOG PS 0-1, disease progression or intolerance to treatment with at least one TKI	ABCP ^a	BCP ^b	19.6
West et al., 2019 ⁵⁴ (IMpower130)	Phase 3 (exploratory)	44	Non-SCC NSCLC harboring <i>EGFR</i> mutation or <i>ALK</i> translocation, stage IV, 18 y or older, ECOG PS 0-1, disease progression, or intolerance to treatment with at least one TKI	Atezolizumab plus CBDCA/ nabPTX	CBDCA/nabPTX	18.5

^aABCP, Atezolizumab plus CBDCA/PTX/bevacizumab.

^bBCP, CBDCA/PTX/bevacizumab.

19del, exon 19 deletion; CBDCA, carboplatin; ECOG, Eastern Cooperative Oncology Group; nabPTX, nab-paclitaxel; PS, performance status; PTX, paclitaxel; RCT, randomized controlled trial; TKI, tyrosine kinase inhibitor.

treatments (pooled HR: 0.97; 95% CI: 0.86–1.10; $p = 0.669$). In addition, in a large-scale observational study, no difference in the PFS when providing erlotinib as first- or third-line pharmacotherapy to patients with *EGFR* mutations were observed.²² On the basis of these results, the best sequence of *EGFR* TKI and cytotoxic chemotherapy treatments is still unclear. *EGFR* TKIs administration resulted in improved quality of life and less toxicity than those obtained with cytotoxic chemotherapy; however, the profiles and degrees of toxicities were different depending on each *EGFR* TKI.^{23,24}

On the basis of a comprehensive evaluation of these results, our guideline recommends the use of *EGFR* TKIs as the first-line pharmacotherapy in patients with NSCLC harboring *EGFR* mutations (particularly exon 19 deletion and L858R mutation).

Recommendations

***EGFR*-Activating Mutations (Exon 19 Deletion and L858R Mutation).** *Good General Condition with Eastern Cooperative Oncology Group Performance Status 0 to 1.* Regarding the question of what is the optimal first-line treatment for patients with Eastern Cooperative Oncology Group performance status (ECOG PS) 0 to 1 (CQ1), the following are the recommendations of the Expert Panel: (1) osimertinib is strongly recommended (R1, evidence level [EL] B, agreement rate [AR] 93%); (2) gefitinib plus carboplatin/pemetrexed is weakly recommended (R2, EL-A); (3) erlotinib plus bevacizumab or ramucirumab is weakly recommended (R2, EL-A); (4) dacomitinib is weakly recommended (R2, EL-B); and (5) gefitinib, erlotinib, or afatinib is weakly recommended (R2, EL-A). Because the comparison in the

clinical trial included in (5) was platinum-doublet chemotherapy, the evaluation criteria for evidence differed from other items.

FLAURA was a phase 3 trial that compared osimertinib with first-generation *EGFR* TKIs (gefitinib or erlotinib) in patients with locally advanced or metastatic NSCLC harboring *EGFR* mutations (exon 19 deletion or L858R mutation). In this trial, the PFS (primary endpoint) was significantly prolonged in the osimertinib arm (HR: 0.46; 95% CI: 0.37–0.57; $p < 0.001$).²⁵ The update, reported in 2019, reported that OS was also significantly improved (HR: 0.80; 95% CI: 0.64–1.00; $p = 0.046$). The subgroup analysis of OS indicated a slight interaction between race and type of *EGFR* mutations. The OS HRs for race were 1.00 (95% CI: 0.75–1.32) and 0.54 (95% CI: 0.38–0.77) in patients with Asian and non-Asian, respectively. In addition, the OS HRs for *EGFR* mutations were 0.68 (95% CI: 0.51–0.90) and 1.00 (95% CI: 0.71–1.40) in exon 19 deletion and L858R mutation, respectively.²⁶ Regarding toxicity, osimertinib tended to have a milder skin rash and liver dysfunction than the first-generation *EGFR* TKIs.

In 2020, two phase 3 trials (NEJ009 and Noronha et al.²⁸) yielded improved PFS and OS when comparing the results of gefitinib and a combination of gefitinib and platinum-based chemotherapy (carboplatin plus pemetrexed) in patients with NSCLC harboring *EGFR* mutations.^{27,28} Both trials consistently yielded improved PFS (pooled HR: 0.50; 95% CI: 0.42–0.59; $p < 0.001$) (Fig. 2A) and OS (pooled HR: 0.58; 95% CI: 0.37–0.92; $p = 0.020$) (Fig. 2B). Adverse events (AEs) of grade 3 or worse were observed more frequently when combining gefitinib with cytotoxic chemotherapy, and their hematologic toxicities were particularly enhanced.

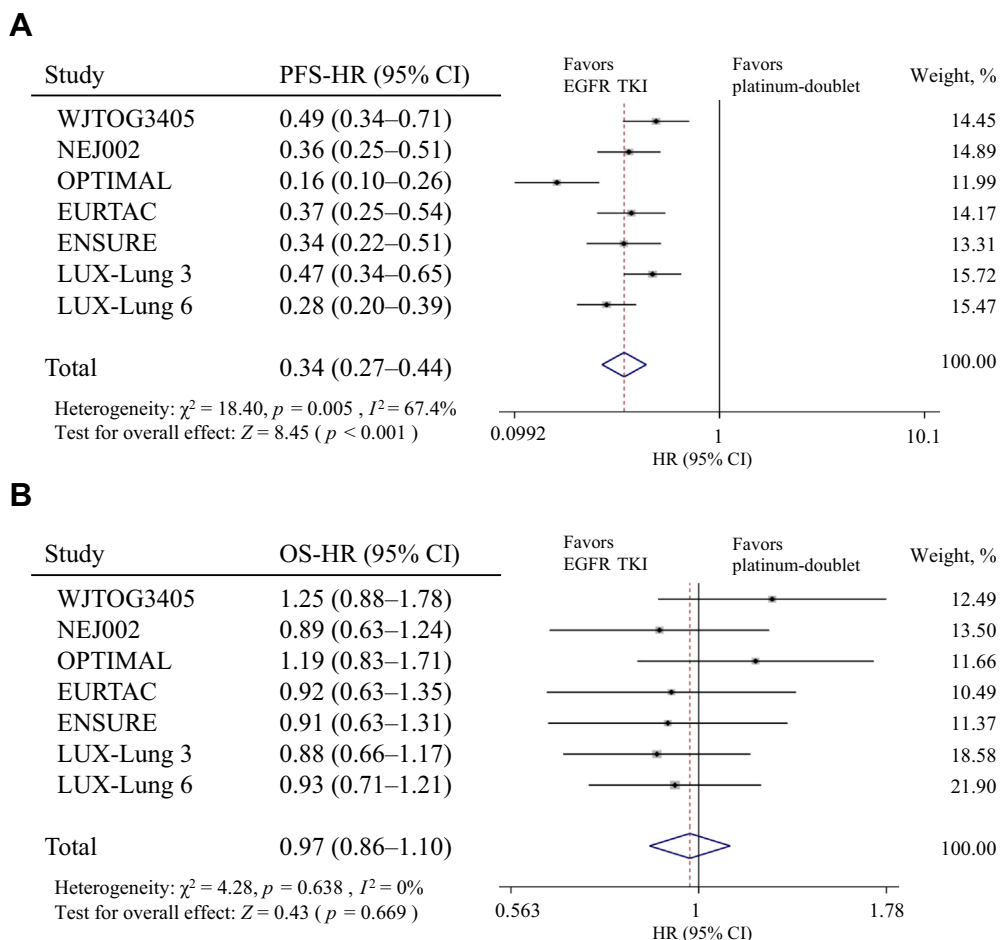


Figure 1. The Forest plot of HR for (A) PFS and (B) OS of patients with NSCLC receiving EGFR TKI versus platinum-based chemotherapy treatments. CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

Four RCTs compared erlotinib plus antiangiogenic agents (bevacizumab or ramucirumab) and erlotinib monotherapy in patients with NSCLC harboring *EGFR*-activating mutations (exon 19 deletion and L858R mutation).²⁹⁻³⁴ Most trials reported the superiority of the PFS with nonheterogeneity ($\chi^2 = 1.77$; $p = 0.622$; $I^2 = 0\%$), and the pooled efficacy was significant (pooled HR: 0.61; 95% CI: 0.51–0.72; $p < 0.001$) (Fig. 3A). However, the OS did not exhibit any obvious improvement (pooled HR: 0.93; 95% CI: 0.74–1.17; $p = 0.528$) (Fig. 3B). In the combination arm, the antiangiogenic drug-related toxicities, such as hypertension, proteinuria, and bleeding, were frequently observed.

ARCHER1050 was a phase 3 trial that compared dacomitinib with gefitinib in patients with stage IIIB/IV NSCLC harboring *EGFR* mutations (exon 19 deletion or L858R mutation). In this trial, patients with brain metastases were excluded. In the dacomitinib arm, the PFS, as a primary end point, was significantly prolonged (HR: 0.59; 95% CI: 0.47–0.74; $p < 0.0001$).³⁵ The OS also

generally exhibited improved trends (HR: 0.760; 95% CI: 0.582–0.993); however, the original hypothesis was rejected by the gatekeeping procedure; therefore, the improvement was not significant.³⁶ Regarding toxicity, dacomitinib was worse than gefitinib in inducing diarrhea, paronychia, and acne-like rash.

None of the other approved EGFR TKIs (gefitinib, erlotinib, and afatinib) exhibited a clear survival advantage. The study CTONG0901, which compared gefitinib and erlotinib, revealed similar survival effects.³⁷ In a randomized phase 2 LUX-Lung 7 trial, which compared afatinib and gefitinib, the PFS was significantly prolonged in the afatinib arm. However, the improvement in OS in the afatinib arm was not significant, and the drug was more toxic than gefitinib.³⁸

The votes of the Expert Panel in this CQ1 with multiple treatment strategies are presented in Supplementary Table 5. Because of insufficient evidence to directly compare the recommended regimens mentioned above, the Expert Panel evaluated them on

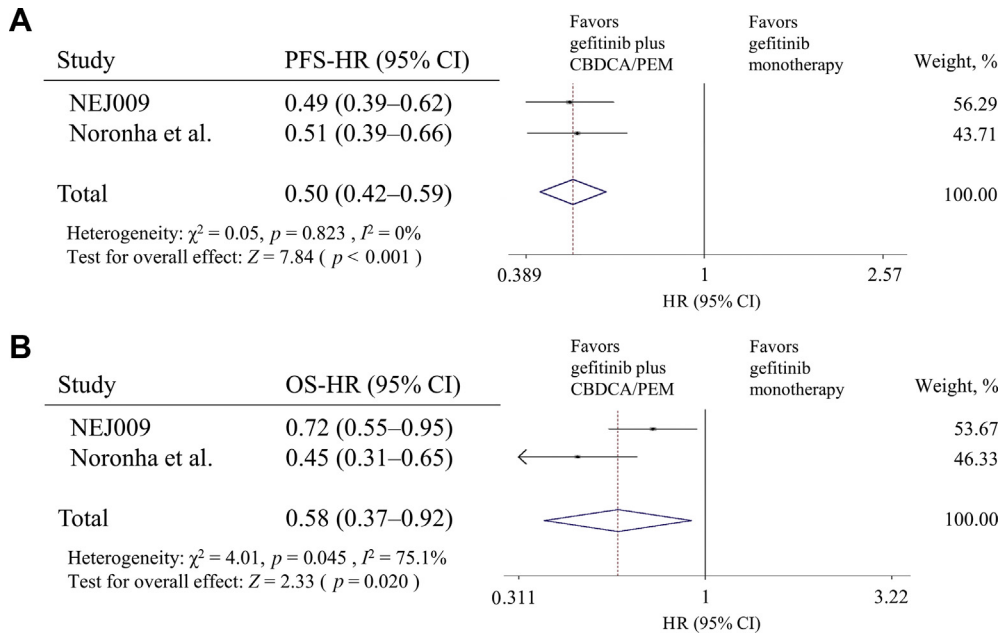


Figure 2. Forest plot of HR for (A) PFS and (B) OS of patients with NSCLC receiving the combination of gefitinib and platinum-based chemotherapy (carboplatin plus pemetrexed) versus gefitinib monotherapy. CBDCA, carboplatin; CI, confidence interval; HR, hazard ratio; OS, overall survival; PEM, pemetrexed; PFS, progression-free survival.

the basis of balancing the benefits and harms of each regimen. Finally, our guideline concludes that osimertinib monotherapy is the most recommended among

patients in good general condition. A combination of EGFR TKI and other agents is also recommended; however, its toxicity should be noted.

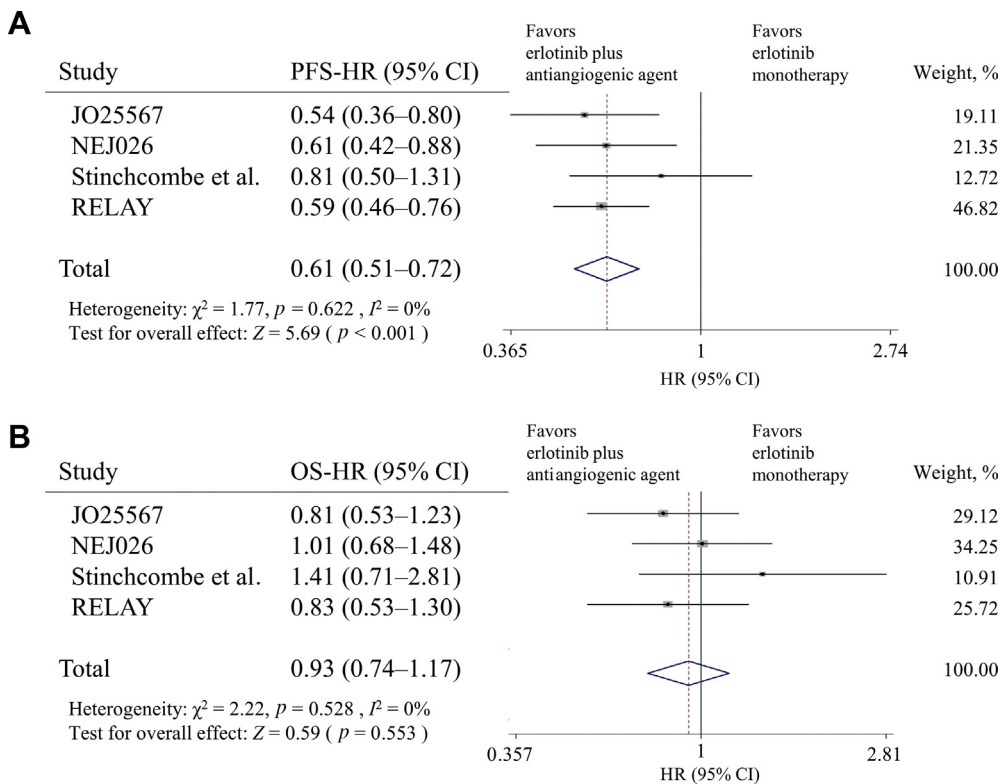


Figure 3. The forest plot of HR for (A) PFS and (B) OS of patients with NSCLC receiving the combination of erlotinib and antiangiogenic agent versus erlotinib monotherapy. CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

Moderate *General Condition* (ECOG PS 2). Regarding the question of what is the optimal first-line treatment for patients with ECOG PS 2 (CQ2), the use of EGFR TKI (gefitinib or erlotinib) is strongly recommended (R1, EL-C, AR 86%). The use of gefitinib plus carboplatin/pemetrexed cannot be determined because of uncertain outcomes.

In two phase 3 trials comparing erlotinib with platinum-doublet chemotherapy, patients with *EGFR*-mutant NSCLC with PS 2 were enrolled at around 6% to 14% of the total population^{14,16,18} Both trials tended to prolong PFS in the erlotinib arm compared with the platinum-doublet arm, albeit in a small number of cases. Gefitinib was safe and effective against patients with poor PS with *EGFR* mutations in two nonrandomized phase 2 trials,^{39,40} whereas afatinib and dacomitinib have not been adequately and prospectively considered. The efficacy of osimertinib in patients with PS 2 has not been confirmed in a reliable study; however, its toxicity other than interstitial lung disease may be milder than that of gefitinib or erlotinib.²⁵

In a phase 3 trial comparing gefitinib plus platinum-based chemotherapy (carboplatin/pemetrexed) and gefitinib monotherapy, patients with NSCLC with PS 2 were included in 21% to 22%.²⁸ A subgroup analysis revealed that the combination arm improved the OS in patients with PS 2 compared with gefitinib monotherapy (HR: 0.57; 95% CI: 0.33–0.98). The evaluation of patients with PS 2 noted AEs greater than grade 3 to be more significantly frequent in the combination treatment than EGFR TKI monotherapy (58% versus 28%).⁴¹

The votes of the Expert Panel in this CQ2, including the two treatment strategies mentioned above, are presented in [Supplementary Table 6](#). In the Expert Panel, the subgroup analysis against PS 2 by Noronha et al.²⁸ was evaluated to have a high risk of bias because of the unclear concealment and incomplete outcome data. Therefore, our guideline recommends EGFR TKI (especially gefitinib, or erlotinib) monotherapy. In contrast, any recommendation for the combination of gefitinib and chemotherapy could not be determined by our consensus.

Poor General Condition (ECOG PS ≥3). Regarding the question of what is the optimal first-line treatment for patients with poor general condition (CQ3), gefitinib is strongly recommended (R1, EL-C, AR 75%).

NEJ001 was a nonrandomized phase 2 trial that evaluated gefitinib monotherapy in patients harboring *EGFR* mutations with poor PS, which included 73% of patients with PS 3 to 4.³⁹ In the PS 3 to 4 group, gefitinib exhibited favorable effects (overall response rate [ORR]: 66%; median PFS: 6.5 mo; median OS: 17.8 mo), improving PS in approximately 80% of this population.

In contrast, two retrospective studies reported that poor PS might be a risk factor for the development of interstitial pneumonia because of gefitinib.^{42,43}

The Expert Panel discussed the pros and cons of the treatment, especially for PS 4. Therefore, gefitinib was recommended in such a population as well. However, it is necessary to thoroughly evaluate whether EGFR TKIs could be expected to improve PS or symptoms.

EGFR Uncommon Mutations. Regarding the question on what is the optimal first-line treatment for patients harboring uncommon *EGFR* mutations with a good general condition (CQ4), the following are the recommendations: (1) EGFR TKIs are weakly recommended in patients harboring uncommon *EGFR* mutations, except for exon 20 insertion and de novo T790M mutations (R2, EL-C, AR 87%); (2) EGFR TKIs are strongly not recommended in patients harboring *EGFR* exon 20 insertion mutations (NR1, EL-C, AR 70%); and (3) osimertinib is weakly recommended in patients harboring de novo T790M mutations (R2, EL-D, AR 67%).

Except for *EGFR*-activating mutations (exon 19 deletion and L858R mutation), uncommon mutations in exons 18 to 21 are generally identified in about 10% of the cases.⁴⁴ The efficacy of EGFR TKIs was slightly inferior in the presence of uncommon rather than activating mutations.⁴⁵ Some of the above phase 3 trials excluded patients with these mutations.^{10,14,16,18} The uncommon mutation is not clearly defined. Therefore, in the present guideline, all mutations in the exons 18 to 21 regions, excluding exon 19 deletion and L858R mutation, are classified as uncommon mutations. The coexistence of tumors with common and uncommon mutations was classified as an uncommon mutation.

The efficacy of EGFR TKIs varied and depended on the type of these uncommon mutations; meanwhile, the ORR was reported as 48.4% in a retrospective analysis.⁴⁵ In the pooled analysis of three prospective trials for uncommon mutations, excluding the T790M mutation and the exon 20 insertion, the use of afatinib resulted in an ORR of 71.1% and a median PFS of 10.7 months.⁴⁶ In a phase 2 trial of osimertinib for the same patients, the ORR was 50%, and the median PFS was 8.2 months.⁴⁷ Because these results had different frequencies and treatment efficacies of uncommon mutations, the Expert Panel concluded that the superiority of each EGFR TKI when treating patients with uncommon mutations, except for T790M and exon 20 insertion, should not be determined.

Exon 20 insertion is rare, and few retrospective studies have reported that the ORRs of EGFR TKIs were less than 10%.^{46,48} Thus, treatment with EGFR TKIs is not recommended as first-line pharmacotherapy.

The detection of de novo T790M mutations in treatment-naïve patients who participated in clinical trials that used EGFR TKIs was extremely rare. In a phase 1 trial that tested osimertinib for treatment of patients with EGFR mutations, a partial response was observed in six of seven (86%) treatment-naïve patients with NSCLC harboring de novo T790M mutations.⁴⁹ Efficacy data were limited.

Regarding whether osimertinib is recommended as second-line treatment for patients harboring EGFR T790M-resistant mutation after the progression of EGFR TKIs (CQ5), the Expert Panel strongly recommended osimertinib (R1, EL-B, AR 100%).

AURA3 was a phase 3 trial that compared osimertinib and platinum plus pemetrexed treatments in patients with NSCLC who progressed after receiving a first- or second-generation EGFR TKIs and acquired T790M resistance mutations. The PFS medians, as the primary endpoint, was 10.1 months in the osimertinib arm and 4.4 months in the platinum plus pemetrexed arm, which were significant (HR: 0.30; 95% CI: 0.23–0.41; $p < 0.001$). In addition, the frequency of grade 3 AEs or greater was lower in the osimertinib rather than the platinum plus pemetrexed treatment group (6% versus 34%).⁵⁰

Cytotoxic Chemotherapy. Regarding the question as to whether cytotoxic chemotherapy is recommended for patients harboring oncogenic driver alterations (CQ6), the Expert Panel concluded that this is strongly recommended (e.g. platinum-doublet) (R1, ELA, AR 100%).

The administration of kinase inhibitor was the best treatment for patients harboring oncogenic driver alterations; however, in the analyzed RCTs, most patients received cytotoxic chemotherapy. According to the post hoc analyses of RCTs, the prognosis of patients receiving cytotoxic chemotherapy was slightly better.^{11,13} The same tendency was observed in a Japanese real-world observational study.⁵¹ If the patient is resistant to osimertinib, or resistant to other EGFR TKIs without T790M-acquired mutation, cytotoxic chemotherapy, such as platinum-doublet, is recommended.

ICI Monotherapy. Regarding the question as to whether ICI monotherapy is recommended for patients harboring oncogenic driver alterations (CQ7), the Expert Panel states that recommendations cannot be determined because of uncertain outcomes; as such, no specific recommendations can be made (EL-B, AR 73%).

Most of the phase 3 trials that evaluated the efficacy of ICI monotherapy as a first-line treatment excluded patients harboring EGFR mutations and ALK fusions. A

meta-analysis of RCTs that compared programmed cell death protein 1/programmed death-ligand 1 (PD-L1) inhibitors with docetaxel as a second-line treatment did not illustrate OS superiority in the EGFR-mutant subgroup (pooled HR: 1.11; 95% CI: 0.80–1.53; $p = 0.54$).⁴ A retrospective study reported that the ORR of programmed cell death protein 1/PD-L1 inhibitors in EGFR-mutant or ALK-positive patients was 3.6%.⁵² The Expert Panel determined that the efficacy of ICI monotherapy on oncogenic driver alterations might be inferior to that of each TKI or platinum-based chemotherapy. The administration of ICI as the first- or second-line treatment is not recommended, although administration as a later-line treatment could be considered. However, evidence supporting the above perspective remains insufficient.

Combination of ICIs and Cytotoxic Chemotherapy. Regarding the question as to whether the combination of ICI and cytotoxic chemotherapy recommended for patients harboring oncogenic driver alterations (CQ8), the Expert Panel states that recommendations cannot be determined because of uncertain outcomes; as such, no specific recommendations can be made (EL-C, AR 64%).

The exploratory analysis of a phase 3 trial (IMpower150) that evaluated the treatment of patients with NSCLC harboring EGFR mutations with PD-L1 inhibitor atezolizumab plus carboplatin/paclitaxel plus bevacizumab indicated that the addition of atezolizumab slightly improved the PFS (HR: 0.61; 95% CI: 0.36–1.03) and OS (HR: 0.61; 95% CI: 0.29–1.28).⁵³ However, it should be noted that the number of cases evaluated was limited to 79 (out of which, exon 19 deletion and L858R mutation were 58). A phase 3 trial (IMpower130) that evaluated the efficacy of atezolizumab plus carboplatin/nab-paclitaxel also conducted an exploratory analysis of EGFR mutations and ALK fusions. According to the Kaplan-Meier curve of that trial, the addition of atezolizumab had a few advantages in PFS and OS.⁵⁴ The Expert Panel pointed this out as a bias because of the nonstratification in subgroup analyses. As with CQ7, the evidence for CQ8 is still inadequate.

Discussion

This set of guidelines has unique features that are unlike that of the European Society for Medical Oncology and National Comprehensive Cancer Network guidelines.^{55–57} First, because of Japan's universal health insurance system, the selection of treatment options was not affected by costs. Second, CQs were specially developed according to the patient's condition, such as the

older adults and those with poor PS. However, we will continue to make yearly revisions and provide recommendations that meet the needs in the actual clinical practice in Japan.

Limitations

The evidence reviewed in the guidelines included some limitations. First, few studies have directly compared the response to EGFR TKIs from different generations. Second, the information about factors that were harmful to patients between the studies, such as patient's reported outcomes and treatment costs, was insufficient. In addition, the results obtained from a unique population, such as the one containing the uncommon *EGFR* mutation or patients with poor PS, relied on nonrandomized or observational studies. Therefore, the Expert Panel made consensus recommendations on the basis of limited evidence from the literature.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at <https://doi.org/10.1016/j.jtocrr.2020.100107>.

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